is one of the group of recited sequences. Claims 2-18, 24-30, 37, 40 and 41 have been amended to correct a typographical error in antecedent basis. Claims 6, 11, 13, 16 and 18 have been amended to recite specific sequence identifiers for the recited amino acid sequences, and to eliminate the term "and/or" and the reference to variants. Claims 7-9 and 20-22 have been amended to recite the specific nucleotides that encode the amino acid sequence, and claims 7-9 have further been amended to eliminate the reference to variants. Support for the recited nucleotides may be found, for example, within SEQ ID NOs:7, 8 and 13. Claims 30 and 40 have been amended to eliminate the reference to binding agents and inhibitors, and to refer instead to antibodies, single chain antigen binding proteins and antigen combining sites. Support for this amendment may be found, for example, in the specification at page 23, lines 15-25 and page 24, line 19. No new matter has been added. Therefore, claims 1-28, 30-31 and 36-41 are now pending.

The Examiner is of the view that claim 6 is not in full compliance with the sequence rules. More specifically, the Examiner has requested the designation of each portion of the recited sequences as a separate sequence. Applicants have amended this claim (as well as claims 11, 13, 16 and 18) accordingly, and Applicants submit that this objection has been obviated.

The Examiner has further requested the insertion of sequence identifiers for Tables III-XI. Applicants have amended the specification to recite sequence identifiers. Applicants submit that this objection has been obviated. More specifically, Applicants submit herewith replacement pages 51-59B, to be substituted for pages 51-59 of the specification as filed. These replacement pages are identical to original pages 51-59, except for the addition of sequence identifiers.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claims 1-31 and 36-41 under 35 U.S.C. §112, first paragraph, for lack of enablement. In particular, the Examiner asserts that the specification does not provide enablement for targeting molecules (TMs) other than native J chains. (The Examiner does agree that the specification is enabling wherein TM comprises a native J chain.) The Examiner is particularly concerned that the claims encompass TMs that are structurally unrelated to J chains or that target molecules other than pIgR. The Examiner is further concerned that there is no teaching of how to noncovalently link a biological agent directly to a J chain.

Applicants respectfully traverse this ground for rejection. Applicants believe that the specification clearly describes modified J chains that function as TMs (*see, e.g.*, the specification at page 13, line 23 - page 15, line 2, as well as Example 1). Nonetheless, to facilitate allowance, Applicants have amended claims 1, 36, 38 and 39 to recite that the polypeptide comprises a J chain or portion thereof that specifically binds to an epithelial basolateral factor. Support for this amendment may be found, for example, in the specification at page 8, lines 29-30, and page 9, lines 11-14. Applicants further believe that methods for noncovalent linkage, which may be used to link a biological agent to a J chain, are well known in the art. Such methods include, for example, adsorption (*see* page 17, line 22 of the specification). Accordingly, Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

The Examiner has rejected claims 7-9, 11 and 20-28 under 35 U.S.C. §112, first paragraph, for lack of enablement. More specifically, the Examiner has noted that these claims recite polypeptides that comprise a nucleotide sequence. Applicants respectfully traverse this ground for rejection. Applicants have amended claims 7-9 and 20-22 to recite that the polypeptides comprise an amino acid sequence encoded by the nucleotides in the recited sequences. Applicants submit that those of ordinary skill in the art would have realized that the polypeptides are intended to be encoded by the recited nucleotide sequences. Further support for this amendment may be found, for example, in the specification at page 41, lines 19-25, as well as Tables III, IX and X. Applicants believe that this ground for rejection was inappropriately applied to claim 11, since all of the SEQ ID NOs in that claim correspond to polypeptide sequences. Accordingly, Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner has issued several rejections under 35 U.S.C. §112, second paragraph, for indefiniteness. In one such rejection, claims 19-28 were rejected because the Examiner believes that the phrase "a sequence recited in" is unclear. The Examiner appears to be concerned that this phrase could encompass portions of the recited sequences. Applicants respectfully traverse this ground for rejection. Applicants have amended claim 19 to replace this phrase with Markush language. In addition, claims 20-22 have been amended to recite that the polypeptide is encoded by specific nucleotides in the identified sequences. Applicants believe that these amendments make it clear that the polypeptides are encoded by the full

recited sequences. Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

In another such rejection, claims 30 and 40 were rejected on the grounds that the terms "binding agent" and "inhibitor" are indefinite. Applicants respectfully traverse this ground for rejection. While Applicants believe that these terms are clearly defined in the specification (*e.g.*, at page 23, lines 14-25 and page 24, lines 6-20), to facilitate allowance Applicants have eliminated these terms from claims 30 and 40, and have substituted therefor the phrase "antibodies, single chain antigen binding proteins and antigen combining sites." Support for this amendment may be found in the specification at page 23, lines 15-25 and page 24, lines 19. Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

In a third rejection under 35 U.S.C. §112, second paragraph, claims 6, 11, 13, 16 and 18 were rejected because the Examiner believes that these claims recite a Markush group in an improper format. This rejection appears to be based on the use of the term "and/or." Applicants respectfully traverse this ground for rejection. While Applicants believe that these claims would be readily understood by those of ordinary skill in the art, Applicants have replaced the term "and/or" with "or." Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

Finally, claims 6-9, 11, 13, 16 and 18 were rejected because the Examiner believes that the phrase "conservative substitutions and/or modifications" is unclear. Applicants respectfully traverse this ground for rejection. Applicants believe that this phrase is sufficiently defined in the specification (*e.g.*, at page 11, lines 23-28) and would be readily understood by those of ordinary skill in the art. Nonetheless, in order to facilitate allowance of these claims, Applicants have removed this phrase from all claims in which it appears. Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 102(B)

Claims 1, 2, 6-18 and 31 were rejected under 35 U.S.C. §102(b) as unpatentable over Ferkol et al. (*J. Clin. Invest. 92*:2394-2400, 1993). In particular, the Examiner asserts that Ferkol et al. teaches a TM that is a variant of a J chain linked to a biological agent.

Applicants respectfully traverse this ground for rejection. Applicants wish to point out that the present invention is based on the surprising discovery that molecules with a

β-sheet and closed covalent loop, such as J chains and derivatives thereof, are capable of specifically binding to a factor preferentially distributed on an epithelial surface and causing the internalization of a linked biological agent. Ferkol et al. does not teach or suggest this aspect of the subject invention. On the contrary, that reference describes the use of an anti-pIgR Fab (IgG) fragment to bind a pIgR. The binding of a Fab fragment to an antigen is known to be mediated by the interaction of amino acids in hypervariable regions with cognate epitopes. This is a fundamentally different type of interaction from that involved in the ability of a β-sheet and closed covalent loop to bind pIgR, and Ferkol et al. does not teach or suggest that their results can be extended to anything other than Fab antigen combining sites.

To clarify the distinction between Fab fragment binding as described by Ferkol et al. and the binding contemplated by the present invention, Applicants have amended claim 1 to recite that the polypeptide comprises a J chain or a portion thereof that specifically binds to an epithelial basolateral factor. Claim 1 has further been amended to recite that the targeting molecule is linked to a peptide sequence that directs delivery of the biological agent to a carcinoma cell, a nucleus or an endoplasmic reticulum. Such a linkage is not disclosed or suggested by Ferkol et al. Support for this amendment may be found, for example, within the specification at page 14, lines 3-4; page 19, line 27 – page 20, line 2; page 20, lines 14-16; and page 70, line 14 – page 72, line 2. Accordingly, Applicants respectfully submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

Claims 1-3, 6-18, 31, 36 and 37 were rejected under 35 U.S.C. §102(b) as unpatentable over Lemaitre-Coelho et al. (*Immunology 43*:261-270, 1981). In particular, the Examiner believes that Lemaitre-Coelho et al. teach a polymeric Fcα, which the Examiner asserts satisfies the TM limitations of claim 1 and contains a protein biological agent that affects the renal system.

Applicants respectfully traverse this ground for rejection. This rejection appears to be based on the view that Fc/alpha-J chain constitutes a TM linked to a biological agent. In such a construct, the Examiner appears to believe that the Fc functions as a biological agent. Applicants disagree with this interpretation. A biological agent is a molecule that is synthesized by a cell or *ex vivo*, or that has an effect on a cell (*see* page 7, lines 21-25, of the specification). Fc fragments are generated *in vitro*, by digestion of antibodies, and are not synthesized by a cell. Further, there is nothing in Lemaitre-Coelho et al. to suggest that the Fc functions as a drug, as suggested by the Examiner, or indeed that is has any biological effect on a cell. Thus, the Fc fails to satisfy the requirements of a biological agent, and Applicants

submit that Lemaitre-Coelho et al. does not disclose a J chain linked to a biological agent. In addition, as discussed above, Applicants have amended claims 1, 19-22, 36, 38 and 39 to recite that the targeting molecule is linked to a peptide sequence that directs delivery of the biological agent to a carcinoma cell, a nucleus or an endoplasmic reticulum. Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. § 103(A)

The Examiner has rejected claims 1-31 and 36-41 under 35 U.S.C. §103(a) as unpatentable over Terskikh et al. (*Molecular Immunology 31*:1313-1319, 1994) and Ferkol et al. (*J. Clin. Invest. 92*:2394-2400, 1993) in view of Morton et al. (*J. Immunol. 151*:4743-52, 1993), Carayannopoulos et al. (*Proc. Natl. Acad. Sci. USA 91*:8348-52, 1994) and Carayannopoulos et al. (*J. Exp. Med. 183*:1579-86, 1996), and further in view of Weissleder et al. (*Antimicrob. Agents Chemother. 39*:839-45, 1995), Janoff et al. (U.S. Patent No. 4,897,384), Shen et al. (U.S. Patent No. 5,254,342), Weiner et al. (U.S. Patent No. 5,366,958) and Pierce Chemical Company Catalog. In particular, the Examiner believes that Terskikh et al. teaches a dimeric IgA that translocates across an epithelial cell monolayer and that Ferkol et al. teaches the use of pIgR for receptor mediated gene transfer. Morton et al. and Carayannopoulos et al. (1994) were cited for the recombinant expression of human IgA, and Carayannopoulos et al. (1996) was cited as disclosing the localization of the Fc receptor binding site on IgA. The Examiner notes that none of these references teach a TM linked to a biological agent, wherein the TM is not a full length dimeric IgA. Nonetheless, the Examiner asserts it would have been obvious to link dimeric IgA (as taught by Terskikh et al. and Ferkol et al.) to a biological agent, and to generate a TM by deleting or mutating the Fc receptor binding site on the IgA (as taught by Morton et al., Carayannopoulos et al. (1994) and Carayannopoulos et al. (1996)). Accordingly, the Examiner asserts that these references, in combination, suggest a TM linked to a biological agent, wherein the TM is not a full length dIgA.

The Examiner believes that the remaining references, taken together, disclose the elected species in which the biological agent is gentamycin, and is linked to the TM via a peptide bond. More specifically, the Examiner is of the view that Weissleder et al. teaches the conjugation of gentamycin, that Janoff et al. teaches uses for gentamycin, Shen et al. teaches receptor-mediated transcytosis of drugs, Weiner et al. teaches targeted drug delivery via fibronectin and the Pierce Chemical Company Catalog teaches linkage of a targeting molecule

to a biological agent via peptide bonds. Accordingly, the Examiner asserts that it would have been obvious to link gentamycin to a TM that is not a full length dIgA via a peptide bond.

Applicants respectfully traverse this ground for rejection. As an initial matter, Applicants believe that those of ordinary skill in the art would appreciate that Terskikh et al. and Ferkol et al. do not disclose a TM according to the present invention. However, to facilitate prosecution, Applicants have amended the claims to eliminate the term "variant." Accordingly, Applicants believe that the cited references, taken alone or in combination, do not teach or suggest a targeting molecule as recited in the pending claims. Further, the Examiner appears to be employing hindsight in this rejection, since the use of a TM to deliver a biological agent across an epithelial barrier was first disclosed in the present application. Accordingly, there would have been no recognition that a TM could provide such a function, and no motivation to combine the large number of cited references. In addition, as discussed above, Applicants have amended claims 1, 19-22, 36, 38 and 39 to recite that the targeting molecule is linked to a peptide sequence that directs delivery of the biological agent to a carcinoma cell, a nucleus or an endoplasmic reticulum. Applicants respectfully submit that none of the recited references, taken alone or in combination, disclose the use of such peptide sequences and that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

DOUBLE PATENTING REJECTIONS

The Examiner has issued a provisional statutory double patenting rejection under 35 U.S.C. §101 with respect to claims 1-31 and 36-41, in view of copending Application Number 08/782,481 ('481 application).

Applicants respectfully traverse this ground for rejection. As noted above, Applicants have amended the present claims to recite that the targeting molecule is linked to a peptide sequence that directs delivery of the biological agent to a carcinoma cell, a nucleus or an endoplasmic reticulum. The currently pending claims in the '481 application do not recite this limitation. Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

The Examiner has further issued several provisional obviousness-type double patenting rejections. Claims 1-31 and 36-41 were rejected over the pending claims of Application Number 08/782,481. In addition, claims 1-31 and 36-41 were provisionally rejected over the claims of Application Numbers 08/782,480, 08/954,211, 09/176,741 and 09/005,167. The Examiner asserts that the claims of these applications are not distinct from

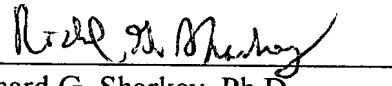
those of the present application in that they appear to be directed to the same J chain TMs and biological agents.

Applicants respectfully traverse this ground for rejection. As noted above, the present claims, as amended, recite that the targeting molecule is linked to a peptide sequence that directs delivery of the biological agent to a carcinoma cell, a nucleus or an endoplasmic reticulum. Of the applications listed above, only 09/005,167 ('167 application) recites such a targeting molecule. The present claims differ from those in the '167 application in that the TMs are linked to a biological agent, rather than an imaging agent. Biological agents (*i.e.*, substances that are derived from a cell or that modify the properties of a cell) are fundamentally different from imaging agents, which are designed to illuminate a physiological function in a patient, while leaving other physiological functions generally unaffected. Accordingly, the claim scope in these applications is different, and Applicants submit that this ground for rejection has been overcome. Withdrawal of this rejection is respectfully requested.

All of the claims remaining in the application (claims 1-28, 30-31 and 36-41) are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If the Examiner does not believe the claims are allowable for any reason, the Examiner is encouraged to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



Richard G. Sharkey, Ph.D.
Registration No. 32,629

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701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031
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